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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/646,363	08/21/2003	Xian-Ming Zeng	NHC19586-USA	8633

530 7590 04/04/2008

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EXAMINER	
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ART UNIT	PAPER NUMBER
1616	
MAIL DATE	DELIVERY MODE
04/04/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/646,363	ZENG, XIAN-MING	
	Examiner	Art Unit	
	JAMES H. ALSTRUM ACEVEDO	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 5-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-3 and 5-19 are pending. Applicant has amended claims 1, 6-9, and 11-12. Applicant has cancelled claim 4. Receipt and consideration of Applicant's amended claims and remarks/arguments, submitted on December 12, 2007 are acknowledged. All rejections not explicitly maintained in the instant office action have been withdrawn per Applicants' claim amendments.

Moot Rejections/objections

All rejections and/or objections of claim 4 cited in the previous office action mailed on August 7, 2007 **are moot**, because said claim has been cancelled.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/10/07 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-9 and 12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 6-9 and 12 of the instant application claim a method of preparing a dry powder inhalation composition comprising (i) a 1st particulate medicament (e.g. an antiinflammatory steroid, such as budesonide) or a pharmaceutically acceptable salt, solvate[1], or salt solvate thereof and (ii) a 2nd particulate medicament (e.g. a bronchodilator, such as formoterol) or a pharmaceutically acceptable salt, solvate, or salt solvate thereof. The instant specification does not disclose, to which solvates or salt solvates of the 1st and 2nd particulate medicaments Applicants are referring. In paragraph [0029], Applicant indicates that the term solvate is inclusive of hydrates, but does not define solvate to be limited to hydrates. The only specific salt solvate mentioned in Applicant's specification is "formoterol fumarate dihydrate", mentioned in paragraph [0030] of Applicant's specification. No other salt solvates are disclosed in Applicant's specification. It is generally accepted in the art that the formation of a particular solvate or hydrate for a given compound or series of compounds is unpredictable (see Vippagunta et al. "Crystalline Solids," *Advanced Drug Delivery Reviews*, **2001**, *48*, pp 18), therefore, the generic reference to a solvate of anti-inflammatory steroids, bronchodilators, formoterol, 1st particulate medicament, or 2nd particulate medicament in the instant specification

[1] Applicant indicates that solvate includes hydrates, but does not define the term solvate to be limited to hydrates.

does not provide adequate written support for claims drawn to any solvate or hydrate of these compounds, with the exception of formoterol fumarate.

Claim Rejections - 35 USC § 103

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-3 and 5-19 **remain rejected** under 35 U.S.C. 103(a) as being unpatentable over Trofast (U.S. Patent No. 6,030,604) and Keller (WO 00/28979, wherein U.S. Patent No. 6,645,466 is being used as the English language equivalent) in view of Ward et al. (U.S. Patent No. 6,616,914) for the reasons of record, which have been restated below.

Applicant Claims

Applicant claims (1) a method of preparing a dry powder inhalation composition comprising the steps of (a) mixing a particulate carrier with a first portion of a first particulate medicament to obtain a first mixture (b) mixing said first mixture with a second particulate medicament to obtain a second mixture, and (c) mixing said second mixture with a second portion of the first medicament to form a dry powder inhalation composition, wherein the ratio

by weight of the 2nd medicament/carrier ratio is less than the ratio by weight of the 1st medicament to the carrier, wherein the particulate carrier has a VMD of from about 50 to about 250 microns and (2) a dry powder inhalation composition made utilizing a method similar to (1), wherein the composition consists of (a) said particulate carrier, (b) said 1st particulate inhalant medicament, and (c) said 2nd particulate medicament.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Keller discloses a dry powder composition with improved moisture resistance in Example 8 consisting of 0.2% w/w formoterol fumarate dihydrate (2nd med.), 0.5 % w/w glycopyrrolate (1st med.), 0.5% w/w magnesium stearate (excipient), and 98.8% w/w of lactose monohydrate (carrier) (Example 8; col. 14, lines 35-41). Both formoterol fumarate dihydrate and glycopyrrolate are known medicaments. Keller states,

> "In principle, **the constituents can be mixed with one another in any desired sequence**, where, however, mixing should expediently be carried out in such a way that the particles of the constituents--apart from the adhesion to the carrier particles--are essentially retained as such, i.e. are not destroyed, for example, by granulation and the like (col. 8, lines 53-59)."

Keller discloses that the dry powder formulations can be used in all customary dry powder inhalers and are particularly advantageously for use in **multidose dry powder inhalers** (i.e. MDPI), which contain a powder reservoir (col. 9, lines 3-8). Keller discloses that it is preferred to use magnesium stearate in dry powder formulations containing a betamimetic (e.g. formoterol), and/or an anticholinergic (e.g. glycopyrrolate), and/or a corticosteroid (e.g. budesonide) (col. 6, lines 52-54). Other suitable medicaments for use in Keller's composition are disclosed in col. 6, lines 13-33). Keller discloses that the ingress of moisture in multidose

dry powder inhalers (MDPI) is a problem because it results in a dramatic fall in the in vitro fine particle dose and fine particle dose of pharmaceutical dry powders contained within said MDPI (col. 3, line 60 through col. 4, line 14).

Trofast discloses dry powder formulations for inhalation (title, abstract) that may be administered using any known dry powder inhaler, such as a **multidose inhaler**, wherein the inhaler may be a **dry powder inhaler** (col. 3, lines 20-23), and said formulations are useful for the treatment of respiratory disorders (e.g. asthma) (col. 3, lines 26-28). Trofast discloses in Example 6 a dry powder composition comprising **5.2 parts formoterol fumarate dihydrate, 896.8 parts lactose monohydrate (carrier), and 98 parts budesonide**, wherein the lactose and formoterol are mixed, micronized, and treated according to the method of WO 95/05805; budesonide is added, and the mixture is remixed, remicronized, and agglomerated. Trofast discloses that when formoterol and budesonide are present in the same dry powder formulation the molar ratio of formoterol to budesonide ranges from 1: 2,500 to 12: 1, preferably 1: 133 to 1: 6 (col. 2, lines 14-49). This corresponds to a formoterol to budesonide mass ratio, based on the molecular masses of formoterol fumarate dihydrate (496.513 g/mol) and budesonide (430.534 g/mol), ranging from approximately 1.153: 2,500 to approximately 13.8: 1, preferably from approximately 1.153: 133 to approximately 1.153: 6.

Ward teaches a method for oral and pulmonary delivery of pharmaceuticals, wherein a powder formulation for use in a dry powder inhaler (DPI) comprises a pharmaceutical, which acts as its own carrier and is present as (a) microfine particles having a diameter in the range of 1-10 microns and **larger carrier particles** that have an **average volume median diameter** of 10-2,000 microns, preferably 30-300 microns, and **most preferably from 50-100 microns in**

diameter, and administration of the composition results in both a rapid onset pharmaceutical effect and a slower onset pharmaceutical effect (title; abstract; col. 2, lines 20-25 and 51-56; and claims 1-23). Ward teaches that suitable medicaments for use in the invented formulations include **beta-agonists** (i.e. a known class of bronchodilators), such as **albuterol**, **anti-inflammatories**, and **drugs for treating COPD** and other diseases (col. 4, lines 21-28). Ward teaches that the invented composition is desirable to improve patient compliance for patients taking more than one pharmaceutical (col. 1, line 60 through col. 2, line 13) and that, in general, inert carrier particles such as lactose upon inhalation administration are caught in the mouth and throat, swallowed, and exert no pharmaceutical effect (col. 3, lines 5-12).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Trofast lacks an explicit teaching about the order of steps used in preparing the dry powders. This deficiency is cured by the teachings of Keller. Trofast lacks the teaching of carrier particles having a volume median diameter ranging from about 50 to about 250 microns. This deficiency is cured by the teachings of Ward.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been obvious to a person of ordinary skill in the art at the time of the invention to combine the teachings of Trofast, Keller, and Ward, because all references teach dry powder formulations for inhalation administration. Per the teachings of Keller, it would have been prima facie obvious to a person of ordinary skill in the art at the time of the instant

invention that one could adjust the order of mixing used to obtain an inhalable dry powder formulation. An ordinary skilled artisan cognizant of Ward 's teachings would have readily recognized that carrier particles having a volume median diameter ranging from about 50 microns to about 250 microns would be swallowed upon inhalation administration. An ordinary skilled artisan in the field of pharmaceutical formulations at the time of the instant invention (e.g. a pharmaceutical formulation scientist) would be capable of formulating an inhalable composition characterized by having a pharmaceutical effect exhibiting rapid onset properties through the use of an inert carrier, such as lactose, having a VMD ranging from 10-2,000 microns, more preferably 30-300 microns, and most preferably 50-100 microns. An ordinary skilled artisan would have had a reasonable expectation of success in modifying Trofast's invented formulations to utilize lactose carrier having an VMD ranging from 30-300 microns, because lactose is a well-known carrier used in inhalation formulations, such as the formulation taught by Trofast, and it is known in the art that inert carriers, like lactose, having a VMD from 30-300 microns are not inhaled and exert no pharmaceutical effect upon administration. Regarding the order in which the different components are combined, Keller teaches that the different ingredients can be mixed in any desired sequence. This teaching encompasses the following sequence of steps: blending a portion of 1st active particles with carrier particles to obtain a 1st mixture; combination of a 2nd active with the 1st mixture to obtain a second mixture; and finally admixture of the remaining 1st active particles to obtain a dry powder formulation. Mixing particulate components to obtain a dry powder composition is known as demonstrated by the cited prior art references.

Regarding claim 4, the amounts of active taught by Keller and Trofast would be sufficient to form a monolayer of each of these onto the carrier particles, the amount of actives taught by both Keller and Trofast meet are sufficient to create a monolayer of active onto the carrier surface as discussed on page 10 of the office action mailed on November 13, 2006. Therefore, an ordinary skilled artisan would have had reasonable expectation that mixing of the actives in the amounts taught by both references would obviously result in a coating of at least a monolayer onto the carrier particles. Regarding the "consisting of" langauge of claim 11 and claims dependent therefrom, Trofast teaches compositions consisting solely of (a) a 1st particulate medicament, (b) a 2nd particulate medicament, and (c) a particulate carrier; Keller is relied upon solely for the teaching of the order of mixing the particulate carriers; Ward is solely relied upon for the teaching of the desirable VMD of particulate carriers used in inhalable powder formulations.

Applicant has presented data in the instant specification (Tables 1-4) demonstrating the homogeneity of dry powders produced using Applicant's claimed method. This data is not convincing regarding the patentability of the claimed method, because it lacks a comparison of Applicant's method with the methods of the prior art. Applicant's claims 1-9 are open to a broad range of first and second medicament amounts and proportions. Even if Applicant's data in Tables 1-4 were somehow indicative of structural modification, this ground of rejection would still be proper because applicant's data was demonstrated with only 100:6 and 200:6 proportions of budesonide and formoterol fumarate dihydrate, wherein the total medicament concentration was in the range of about 5 wt%. In other words, Applicant's data is not commensurate in scope with what is being claimed in the cited claims, because these claims recite broad ranges and

claim 10 is not limited to a specific 1st and 2nd medicament mixed with carrier. Claims 1-6, 8, 10, and 16-19 are readable on (i) structurally different medicaments, (ii) much higher or lower total concentrations of medicaments, and (iii) much lower or higher weight ratios of first medicament to second medicament, e.g. 100,000,000:1 or 1:0.99,999. The term "bronchodilator" may refer to a broad range of structurally different compounds (e.g. betamimetics and anticholinergics), which although exhibiting bronchodilating effects have different mechanisms of action and secondary biological activities. The term anti-inflammatory steroid" is also broad and can refer to a great variety of compounds having a steroidal core, but differing in the degree, and sometimes the kind of biological activity exhibited, in addition to anti-inflammatory effects. Similarly, claims 7 and 9 are readable on compositions with (i) structurally different 2nd medicaments (claim 7) or 1st medicaments (claim 9), (ii) much higher or lower total concentrations of medicaments, and (iii) much lower or higher weight ratios of 1st medicament to 2nd medicament. Trofast's disclosed method of mixing the composition constituents would necessarily produce a dry powder that cannot be distinguished from the dry powder encompassed by applicant's broad claim language. These data do not demonstrate that the prior art methods do not yield dry powder formulations exhibiting the same or substantially similar physical properties/characteristics. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments filed 12/10/2007 have been fully considered but they are not persuasive. Applicants traversed the instant rejection by arguing that (1) Trofast teaches that all ingredients have a particle size of less than 10 microns, (2) Ward allegedly teaches away from Applicant's invention because Ward focuses on compositions in which drug particles are function as both carrier and fine particles adsorbed onto said carrier; (3) the prior art does not explicitly teach the formation of a monolayer; and (4) Applicant has identified a problem of forming a ternary mixture.

The Examiner respectfully finds Applicant's arguments unpersuasive. Regarding (3), the teaching of Keller that the ingredients may be mixed in any order would lead the ordinary skilled artisan to modify the order and thus obtain the order of the steps recited in the claimed method through optimization. Regarding (4), Applicant's comments that the order is critical to obtain particles with specific properties is found unpersuasive, because Applicant has provided no data in the instant specification or in declaration format demonstrating the criticality of the order of steps. Furthermore, regarding the alleged problem, it is unclear from Applicant's statements what the actual problem was that Applicant's method allegedly solves. The mere allegation that Applicant's perceived a problem without demonstration that there was actually a problem needing resolution is mere argument and is unpersuasive. Regarding (2), Ward was clearly relied upon as a secondary reference to demonstrate what was well known and conventional in the art, namely that it was common to use inert carriers having a VMD of about 50 to about 250 microns. Regarding (1), Applicants comments rest on the implication that an ordinary skilled artisan would not have recognized the latent advantages of utilizing non-respirable carrier

particles, such as, the lowered likelihood of irritation of the pulmonary tissue as a result of contacting said tissue with less foreign material, especially wherein the individual inhaling the composition were lactose intolerant.

Conclusion

Claims 1-3 and 5-19 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, 9:00-6:30, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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